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A METHOD FOR PRODUCING s-TRIAZOLO(1.5-a)PYRIMIDINES SUBSTITUTED IN POSITION 7 BY BASIC GROUPS

A second copy of Patent No. 55 956 has appeared. (Partially rescinded in accordance with §6, paragraph 1 of the Amended Law on Patenting)

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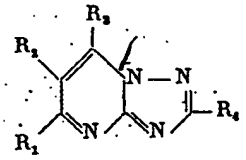
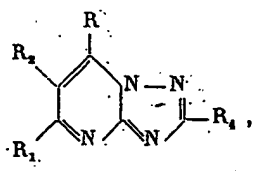
The invention concerns a method for producing s-triazolo(1,5-a)pyrimidines of general formula I substituted in position 7 by basic groups, and their salts.



In this formula R_1 and R_4 mean hydrogen atoms, alkyl residues of chain length C_1-C_4, alkoxyalkyl residues, halogen atoms or aralkyl aryl residues optionally substituted in the nucleus, where R_1 and R_4 can be different. R_2 represents a hydrogen atom, a halogen atom, a lower alkyl, alkenyl, aralkyl or aryl group. R_3 means a free amino group or amino group substituted by the same or different residues, where these residues can be alkyl, cycloalkyl, alkenyl, hydroxyalkyl, alkylaminoalkyl, alkoxy groups, or also aryl or aralkyl groups that are optionally substituted or contain heteroatoms. R_3 can also mean substituted hydrazino or guanidino groups or can be a basically substituted alkoxy group with a normal or branched alkylene chain of 2-4 carbon atoms, in which the basic residue can carry the substituents indicated above.

Such compounds of general formula I, in which R_1 is a methyl residue, R_2 and R_4 represent hydrogen atoms and R_3 represents basic residues, insofar as that they are already known, are prepared by the reaction of 5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine with the corresponding amines in an alcohol solution.

It was surprisingly found that the basically substituted s-triazolo(1,5-a)pyrimidines in an animal test show coronary vessel dilating effect previously not described in this class of compounds and superior to the known compounds of the same direction of effect. The tests are carried out on isolated mammal parts by the method of Langendorff (Pflügers Archiv 61, 219 (1895), in the modification of Ryser and Willbrandt (Arch. int. pharmacodyn.) XCVI 131 (1953)). It turns out that among other things, the compounds 2,5-dimethyl-7-furfurylamino- or 5-methyl-7-diethylamino- or 5-methyl-7-benzylamino-s-triazolo(1,5-a)pyrimidine show coronary vessel dilating effect that is 10-20 times that of euphyllin and theocor. In tests on intact animals, in which the blood flow through the coronary arteries is measured on an unopened coronary vessel with a Nycotron flowmeter, an initial increase of the flow that is 2-3 times the norm for a period of 4-5 min results from a dosage of 1 mg/kg and a persistent increase of the coronary flow by a factor of 1.2 to 1.5 times the norm takes place for about 200 min. Comparable measurements with prenylamine show clearly lesser effects. These compounds should therefore be drawn upon for treatment of coronary vessel diseases. The new compounds are obtained in accordance with the invention if substances of the general formula II



in which R is a halogen atom, a mercapto, alkylmercapto or alkoxy group, R_1, R_2 and R_4 have the meanings given above, are reacted with compounds of the general formula R_3H or $R_3(CH_2)_nONa$ (n = 2,3), in which R_3 has the meaning given above. These reactions are carried out in a substantially known way, by reacting compounds of the general formula II in which R stands for a chlorine or a bromine atom, with amines at room temperature up to the boiling point of the solvent or of the amine, which is used in an excess amount. Water, water-alcohol mixtures, also benzene, dioxane or chloroform are used as solvents. The use of water as solvent allows a particularly simple and elegant conduct of the reaction and the preparation of the desired basically substituted compound from the halogen compound without its prior isolation. To trap the halohydric acid released in the reaction the amines, triethylamine or alkali carbonates, which are used in an excess quantity, are necessary. The further processing of the reaction products takes place in the usual way, by separating the end products from the halogen compounds that have formed and purifying them by recrystallization, extraction or distillation. The synthesis of the basically substituted s-triazolo(1,5-a)pyrimidines can also be carried out so that compounds of general formula II, in which R means a mercapto, alkylmercapto or alkoxy group, are reacted with the amines of the general formula R_3H, used in an excess amount, preferably at the boiling point of the solvent, for example, ethanol, dioxane. In this case hydrogen sulfide or alkylmercaptan is separated, or the alcohol is cleaved off, and the end product remains in the solution, and is purified as indicated above. The basically substituted alkoxy compounds are prepared by reacting the compounds of general formula II in which R stands for a chlorine or bromine atom with the sodium compounds of the amino alcohols. The amino alcohol used in an excess serves as solvent. The resulting compounds are purified as described above.

The substituted 7-chloro- or 7-bromo-s-triazolo(1,5-a)pyrimidines that are required as starting products are prepared by reacting the 7-hydroxy compounds with a phosphorus halide in the presence of N,N-dimethylaniline or N,N-dimethylformamide. The substituted 7-mercapto-s-triazolo(1,5-a)pyrimidines are obtained in a substantially known way by reacting the halogen compound with thiourea followed by alkaline hydrolysis or by thionation of the 7-hydroxy compounds with phosphorus pentasulfide. The subsequent reaction with alkylation agents yields the 7-alkylmercapto-s-triazolo(1,5-a)pyrimidines, while the 7-alkoxy compounds are prepared from the halogen compounds by means of alkali alcoholates. The required 7-hydroxy-s-triazolo(1,5-a)pyrimidines, insofar as that they are not known [sic] compounds, are obtained in the usual way by condensation of an optionally substituted 5-amino-1,2,4-triazole with an optionally substituted 1,3-dicarbonyl compound. The compounds that are obtained can be converted to their salts by treatment with acids.

The method in accordance with the invention is illustrated by means of the following examples. The temperatures are given in degrees Celsius.

Example 1

5.1 g 7-chloro-s-triazolo(1,5-a)pyrimidine are held at slight reflux for 5 h in 50 cm^3 water containing 9.6 g diethylamine. The reaction solution is evaporated out under a vacuum and the residue is extracted with petroleum ether. Upon recrystallization from n-heptane one obtains 3 g colorless crystals of 7-diethylamino-s-triazolo(1,5-a)pyrimidine, m.p. 68°C.

Example 2

4.6 g 7-chloro-s-triazolo(1,5-a)pyrimidine are heated in 50 cm^3 water containing 6.4 g benzylamine for 5 h while stirring and at reflux. Then the reaction solution is cooled, the crystallizate is suctioned out and the residue recrystallized from alcohol. The resulting 7-benzylamino-s-triazolo(1,5-a)pyrimidine (5.2 g) melts at 216-217°C.

Example 3

8.8 g 2-ethyl-5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine are held at slight reflux while stirring for 2.5 h in 50 cm^3 water containing 7.5 g diethylamine. The reaction solution is concentrated until dry and the residue is mixed with acetone. The hydrochloride remains undissolved. After evaporating out the acetone the remaining liquid is distilled and the distillate recrystallized from ether. One obtains 5.9 g colorless crystals of 2-ethyl-5-methyldiethylamino-s-triazolo(1,5-a)pyrimidine, m.p. 61-63°C.

Example 4

2.5 g furfurylamine are added to a solution of 4 g 5-methyl-6,7-dichloro-s-triazolo(1,5-a)pyrimidine in 50 cm^3 ethanol. The mixture is heated at reflux for 3 h on a steam bath, then vacuum dried and the residue is recrystallized from water/dioxane. One obtains 4.5 g 5-methyl-6-chloro-7-furfurylamino-s-triazolo(1,5-a)pyrimidine, m.p. 163°C.

Example 5

4.6 g 5-methyl-6-bromo-7-chloro-s-triazolo(1,5-a)pyrimidine are held at reflux while stirring for 5 h in 20 g diethylamine. Then the excess diethylamine is distilled out, the residue is mixed with water and suctioned out. The insoluble product is recrystallized from gasoline. The resulting 5-methyl-6-bromo-7-diethylamino-s-triazolo(1,5-a)pyrimidine (3.8 g) has a melting point of 84-86°C.

Example 6

1.2 g metallic sodium are dissolved in 60 g diethylaminoethanol. Then 12.5 g 5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine are added and the mixture is heated for 3 h at a bath temperature of 130-140°C. The excess diethylaminoethanol is distilled out under a vacuum and the residue is extracted with n-heptane. Yield: 8.5 g. 5-Methyl-7-(β-diethylaminoethoxy)-s-triazolo(1,5-a)pyrimidine melts at 113-114°C.

Example 7

7.6 g 2-isopropyl-5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine and 6.5 g piperidine are held in 50 cm^3 water for 2.5 h at reflux. Then the product is vacuum dried, recrystallized with n-heptane or distilled in a high vacuum at $bp_{0.6}$ 200-202°C. One obtains 3.5 g 2-isopropyl-5-methyl-7-piperidino-s-triazolo(1,5-a)pyrimidine, m.p. 73-75°C.

Example 8

8.4 g 5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine are dissolved in 75 cm^3 ethanol. 5.5 g triethylamine and 4.5 g n-amylamine are added and the mixture is heated for 5 h at reflux on a steam bath. The reaction solution is concentrated in a vacuum and extracted with n-heptane. Recrystallized from n-heptane, 8 g of 5-methyl-7-n-amylamino-s-triazolo(1,5-a)pyrimidine with a melting point of 111-112°C are obtained.

Example 9

5 g 2-(3',4',5'-trimethoxyphenyl)-5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine are heated in 75 cm^3 butanol containing 3.5 g piperidine for 10 h while stirring and at reflux. The excess n-butanol is distilled out in a vacuum, the residue is suctioned out, and recrystallized from isopropanol. 2.3 g 2-(3',4',5'-trimethoxyphenyl)-5-methyl-7-piperidino-s-triazolo(1,5-a)pyrimidine, m.p. 186-187°C, are obtained.

Example 10

5.7 g 5-phenyl-7-chloro-s-triazolo(1,5-a)pyrimidine and 5.3 g diethanolamine are held in 50 cm^3 butanol for 5 h at reflux. Then this solvent is distilled out under a vacuum, the residue is dissolved in dilute acetic acid, filtered and the filtrate is adjusted to pH 5 with a soda solution. The oil that forms becomes solid after a little time. Recrystallized from water, 6.2 g 5-phenyl-7-diethanolamino-s-triazolo(1,5-a)pyrimidine are obtained as colorless crystals, which melt at 163-165°C.

Example 11

3.7 g 2-phenyl-5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine and 2.7 g piperidine are added to 50 cm^3 butanol. After 5 h of stirring and heating to reflux the excess n-butanol is distilled out and the residue is extracted with gasoline. The resulting 2-phenyl-5-methyl-7-piperidino-s-triazolo(1,5-a)pyrimidine (6 g) melts at 174-175°C.

Example 12

6.4 g o-chloroaniline and 4.3 g 5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine are carefully heated on a water bath. A vigorous reaction takes place and the reaction mixture fuses. The resulting melt is extracted with boiling water and recrystallized from isopropanol/water. Yield: 4.5 g 5-methyl-7-(o-chloroanilino)-s-triazolo(1,5-a)pyrimidine, m.p. 177°C.

Example 13

4.3 g 5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine and 4.2 g p-aminobenzoic acid ethyl ester are heated at reflux for 5 h in 50 cm^3 ethanol. Then the ethanol is distilled out, the residue is mixed with water, suctioned out and recrystallized from toluene. One obtains 7-(p-carbethoxyanilino)-5-methyl-s-triazolo(1,5-a)pyrimidine, m.p. 185°C.

Example 14

6.5 g N,N-diethylpropylenediamine, 4.6 g 5-methyl-6-bromo-7-chloro-s-triazolo(1,5-a)pyrimidine are heated at reflux for 5 h in 50 cm^3 ethanol. The mixture is concentrated under a vacuum, mixed with water, the residue is recrystallized from water/alcohol. The N,N-diethyl-N'-[5-methyl-6-bromo-s-triazolo(1,5-a)pyrimidinyl(7)]propylenediamine has a melting point of 120°C.

Example 15

3.6 g 5-methyl-7-methylmercapto-s-triazolo(1,5-a)pyrimidine, 4.2 g benzylamine and 50 cm^3 isopropanol are heated at reflux until methyl mercaptan formation stops. It is allowed to cool, [then] it is suctioned out, recrystallized from water/isopropanol. 2.5 g 5-methyl-7-benzylamino-s-triazolo(1,5-a)pyrimidine, m.p. 162-163°C, are obtained.

Example 16

2.7 g 2,5-dimethyl-7-ethoxy-s-triazolo(1,5-a)pyrimidine, 6 g furfurylamine and 10 cm^3 isopropanol are allowed to stand for 2 days at room temperature. The precipitate that forms is suctioned out and recrystallized from water/isopropanol. One obtains 2.5 g 2,5-dimethyl-7-benzylamino-s-triazolo(1,5-a)pyrimidine, m.p. 189-190°C.

Example 17

3.4 g 2,5-dimethyl-7-ethoxy-s-triazolo(1,5-a)pyrimidine, 12 g benzylamine and 10 cm^3 isopropanol are heated at reflux for 3 h. The isopropanol is distilled out. The product is recrystallized from water/isopropanol, producing 3 g 2,5-dimethyl-7-benzylamino-s-triazolo(1,5-a)pyrimidine, m.p. 162-163°C.

Example 18

2.7 g 2,5-dimethyl-7-ethoxy-s-triazolo(1,5-a)pyrimidine, 5 g piperidine and 10 cm^3 isopropanol are allowed to stand for 2 days at room temperature. Then the reaction solution is concentrated. The residue is suspended in a little water, dissolved by adding hydrochloric acid, filtered and the base is precipitated as an oil that slowly solidifies through the addition of 25% potassium hydroxide. Recrystallized from n-heptane, 2.7 g 2,5-dimethyl-7-piperidino-s-triazolo(1,5-a)pyrimidine, m.p. 93-94°C, is obtained.

Example 19

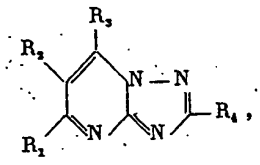
8.4 g 5-methyl-7-chloro-s-triazolo(1,5-a)pyrimidine are suspended in 30 cm^3 water and 7.3 g diethylamine are added. After heating for 2 h while stirring the reaction mixture is concentrated under a vacuum. The residue is recrystallized from n-heptane. One obtains 8.1 g 5-methyl-7-diethylamino-s-triazolo(1,5-a)pyrimidine, m.p. 103-104°C. The hydrochloride, prepared in the usual way, has a melting point of 212°C.

Example 20

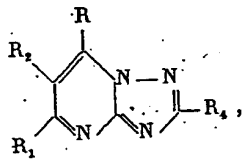
8.4 g 2,5-dimethyl-7-chloro-s-triazolo(1,5-a)pyrimidine are suspended in 25 cm^3 water and 7.3 g isobutylamine are added by drops. Then the mixture is heated for 2 h, concentrated under a vacuum, and the residue is recrystallized from gasoline. The 2,5-dimethyl-7-isobutylamino-s-triazolo(1,5-a)pyrimidine (5 g) melts at 97-98°C. By adding an ether solution of HCl to the solution of the compounds in acetone one obtains the hydrochloride, m.p. 148°C (butanol/ether).

Claims

1. A method for producing s-triazolo(1,5-a)pyrimidines of general formula I substituted in position 7 by basic groups, and their salts



in which R_1 and R_4 mean hydrogen atoms, alkyl residues of chain length C_1-C_4, alkoxyalkyl residues, halogen atoms or aralkyl or alkyl groups optionally substituted in the nucleus, R_2 means a hydrogen or halogen atom, a lower alkyl, alkenyl, aralkyl or aryl group. R_3 means a free amino group or amino group substituted by like or different residues, where these residues can be alkyl, cycloalkyl, alkenyl, hydroalkyl, alkylaminoalkyl, alkoxy groups, or also aryl or aralkyl groups optionally substituted or containing heteroatoms, also an optionally substituted hydrazine, guanidino residue or a basically substituted alkoxy residue with a normal or branched alkylene chain of 2-4 carbon atoms, in which the basic residue can carry the above substituents, which is characterized by the fact that triazolo(1,5-a)pyrimidines of the general formula II



(II)

in which R stands for a halogen atom, a mercapto, alkylmercapto or alkoxy group, R_1, R_2 and R_4 have the meanings given above, are reacted with compounds of the general formula R_3H or alcoholates of the general formula $R_3(OH_2)_nONa$, in which n can take on values of 2, 3 and 4, and R_3 can have the above meaning, in the presence or absence of solvents and in the presence of acid-binding agents like amines or alkali carbonates.

2. A method as in Claim 1, which is characterized by the fact that the reactions of the compounds of the general formula II, in which R stands for a halogen atom, with compounds of the formula R_3H, are preferably carried out in water or water-alcohol mixtures at temperatures between 0°C up to the boiling point of the solvent, and the resulting bases are converted to their salts by treatment with acids.